AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 01: Arthritis and Nontraumatic Joint Disease

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290-2010-00006-C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Financial Disclosure Statement

None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 18,000 leads about potential topics has resulted in identification and tracking of about 2,000 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 550 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 150 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists the single topic for which (1) at least preliminary phase III data were available; (2) information was compiled before November 4, 2014, in this priority area; and (3) we received five to seven sets of comments from experts between January 1, 2013, and November 13, 2014. (Ten topics in this priority area were being tracked in the system as of November 4, 2014.) One topic emerged as having potential for high impact on the basis of experts' comments and their assessment of potential impact. This topic is noted by an asterisk in the table below. Readers are encouraged to read the detailed information on the intervention that follows the Executive Summary.

Priority Area 01: Arthritis and Nontraumatic Joint Disease

Topic	High-Impact Potential
1. *Lesinurad for treatment of hyperuricemia and allopurinol-refractory gout	Lower end of the high-impact-potential range

Discussion

Prior High Impact Topics Archived Since the June 2014 Report

- **Autologous mesenchymal stem cell therapy for osteoarthritis:** In the June 2014 High-Impact Interventions report, this topic was deemed by experts commenting to have potential for high impact (lower on the potential high-impact-potential scale). We have archived this topic after tracking it in the system since March 3, 2011; the intervention has diffused, although payers generally are not paying for it, so patients are paying out of pocket.
- **Autologous platelet-rich plasma therapy for osteoarthritis:** In the June 2014 report, this topic was deemed by experts commenting to have potential for high impact (lower on the potential high-impact-potential scale). We have archived this topic after tracking it in the system since March 4, 2011;the intervention has diffused and is available at many clinics. However, payers generally are not reimbursing for it, so patients are paying out of pocket.

Intervention with Potential for High Impact

Gout is the most prevalent form of inflammatory arthritis and is associated with impaired health outcomes and worsened quality of life. According to data from the U.S. National Health and Nutrition Examination Survey 2007–2008, about 8.3 million adults have gout. Elevated serum uric acid (sUA) levels are thought to be the most important risk factor for the development of gout, which can result in monosodium urate crystals forming and depositing in and around joints, leading to acute flares and inflammation. Uncontrolled gout can lead to accumulation of tophi, leading to chronic pain, joint erosion, and limited mobility. Risk factors for developing gout include obesity, hypertension, alcohol consumption, diuretic use, and a diet rich in fructose, meat, seafood, and vegetable purines. Additionally, patients with chronic hyperuricemia have an increased risk of cardiovascular disease, kidney dysfunction, and metabolic syndrome. Current treatment options for reducing hyperuricemia in patients with gout include the xanthine oxidase inhibitors allopurinol and febuxostat, which decrease uric acid production.

Lesinurad for Treatment of Hyperuricemia and Allopurinol-Refractory Gout

- **Key Facts:** Hyperuricemia is believed to be the most important risk factor for developing gout. About 47% of patients with gout do not achieve target goals for sUA levels (<6 mg/dL) with the standard of care, the xanthine oxidase inhibitors allopurinol and febuxostat. Only about 30% of patients achieve overall gout control, so a significant unmet need exists for more effective treatments. About 90% of patients with gout are thought to have insufficient excretion of uric acid due to genetic defects in renal transporters of uric acid, including the human urate transporter 1 (URAT1), which is involved in uric acid reabsorption. By selectively inhibiting URAT1, lesinurad is thought to promote urinary excretion of uric acid leading to improvements in hyperuricemia. In phase III clinical trials, significantly more patients treated with lesinurad in combination with a xanthine oxidase inhibitor achieved target sUA levels than patients given a xanthine oxidase inhibitor alone. Additionally more patients with gout and an intolerance or contraindication to a xanthine oxidase inhibitors who were given lesinurad as monotherapy achieved target sUA levels than did those given placebo. Patients given lesinurad as monotherapy were more likely to experience serum creatinine elevations and renal adverse events, including serious events, than patients given a placebo. Other adverse events commonly reported in patients treated with lesinurad monotherapy included constipation, diarrhea, and nausea. When lesinurad was combined with xanthine oxidase inhibitors, commonly reported adverse events were arthralgia, back pain, nasopharyngitis, and upper respiratory tract infection.

  Four phase III trials on lesinurad have been completed, and two phase III extension trials are ongoing. The company is preparing U.S. Food and Drug Administration (FDA) regulatory submissions for lesinurad (200 mg) as a once-daily combination therapy for treating gout.

  Our searches found no information regarding the expected cost of lesinurad. However, one financial analyst predicted sales of lesinurad could reach $582 million by the year 2020. An estimated 10% of patients with chronic gout could be prescribed lesinurad, according to an April 2012 survey of rheumatologists in the United States performed by health care consultant Decision Resources Group. If approved for marketing, lesinurad would be covered by third-party payers similar to other uric acid–lowering drugs for treating or preventing gout, although if the drug is more costly than alternatives, prior authorization and a tiered approach would likely be used.

- **Key Expert Comments:** Experts commenting on this intervention stated that a significant unmet need exists for new treatment options to help patients with gout improve the management of their sUA levels. However, this need could be overstated by the manufacturer's estimates. Many treatment options are available to address acute flares and manage chronic gout. However, few agents are available to address the underlying mechanisms leading to gout, the experts thought. Lesinurad demonstrates potential for reducing sUA levels in combination with xanthine oxidase inhibitors or as monotherapy in patients intolerant to xanthine oxidase inhibitors, the experts thought. However, they warned, lesinurad uptake could be limited by adverse events, such as kidney complications, which will continue to be elucidated in ongoing clinical trials.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Gout Intervention

Lesinurad for Treatment of Hyperuricemia and Allopurinol-Refractory Gout

Intervention: Hyperuricemia is thought to be the most important risk factor for developing gout.[1] About 47% of patients with gout do not achieve target goals for serum uric acid (sUA) levels (<6 mg/dL) with the standard of care, the xanthine oxidase inhibitors allopurinol and febuxostat. Also, only about 30% of patients achieve overall gout control, suggesting an unmet need exists for additional options for gout control.[2]

About 90% of patients with gout purportedly have insufficient excretion of uric acid, which could be due to genetic defects in renal transporters of uric acid.[3] About 70% of uric acid excretion occurs in the kidney.[1] Human urate transporter 1 (URAT1) is an organic anion transporter involved in controlling the reabsorption of uric acid from the proximal renal tubules. Lesinurad is a selective inhibitor of URAT1 that purportedly promotes urinary excretion of uric acid leading to improvements in hyperuricemia.[4] Because lesinurad purportedly improves excretion of sUA, it is thought to be complementary to xanthine oxidase inhibitors, which decrease uric acid production.[3] In phase III trials, lesinurad was administered 200 or 400 mg, once daily, orally, in combination with allopurinol or febuxostat,[5,6] or 400 mg, once daily, as monotherapy in patients with an intolerance or contraindication to xanthine oxidase inhibitors.[7]

Clinical trials: Four phase III trials have been completed that evaluated lesinurad in combination with allopurinol or febuxostat, or as monotherapy in patients unable to tolerate xanthine oxidase inhibitors.

In two replicate phase III trials, CLEAR 1 (n=603) and CLEAR 2 (n=610), patients received lesinurad 200 mg or 400 mg or placebo daily in combination with allopurinol. Patients had sUA levels of 6.5 mg/dL or higher at screening, were on stable allopurinol doses (≥300 mg or ≥200 mg in patients with moderate renal impairment), and had a history of at least 2 gout flares in the prior 12 months. In the CLEAR1 trial, patients given lesinurad 200 mg or 400 mg, and 54% and 59%, respectively, achieved the sUA target of less than 6.0 mg/dL by month 6, compared with 28% of patients treated with allopurinol and placebo ($p<0.0001$).[5] In the CLEAR 2 trial, patients were also treated with lesinurad 200 mg or 400 mg, and 55% and 67%, respectively, achieved the sUA target by month 6, compared with 23% of patients treated with allopurinol and placebo ($p<0.0001$).[5] Combination therapy in both trials did not significantly reduce the reported number of gout flares or number of patients with complete tophus resolution.[8]

In the phase III, randomized, double-blind CRYSTAL trial (n=324), patients with gout, sUA levels of 6.0 mg/dL or more, and at least one measurable tophus received lesinurad 200 mg or 400 mg in combination with oral febuxostat (80 mg) or febuxostat with placebo. Data reported by the manufacturer showed that more patients treated with lesinurad and febuxostat achieved the target sUA-level goal of less than 5.0 mg/dL at month 6 than patients treated with febuxostat alone ($p<0.0001$). Patients treated with lesinurad 200 mg and febuxostat did not achieve a statistical improvement at month 6 ($p=0.13$).[6]

In the phase III, randomized, double-blind LIGHT trial (n=214), patients with gout, sUA levels of 6.5 mg/dL or higher, and an intolerance or contraindication to a xanthine oxidase inhibitor were given lesinurad 400 mg or placebo, once daily. Data from the manufacturer showed a significantly higher proportion of patients receiving lesinurad achieved the sUA-level goal of less than 6.0 mg/dL at 6 months than did patients given a placebo.[7] Monotherapy lesinurad resulted in more patients experiencing elevated serum creatinine levels and renal adverse events, including serious events, than patients given placebo. Other adverse events commonly reported in the lesinurad monotherapy group included constipation, diarrhea, and nausea.[7] Some preliminary evidence suggests lesinurad

could increase the risk of renal complications.[9] The most common adverse events reported in patients taking lesinurad with allopurinol in the CLEAR1 and CLEAR2 studies were back pain, nasopharyngitis, and upper respiratory tract infection.[6] The most common adverse events reported in patients given lesinurad and febuxostat during the CRYSTAL trial were arthralgia, nasopharyngitis, and upper respiratory tract infection.[6]

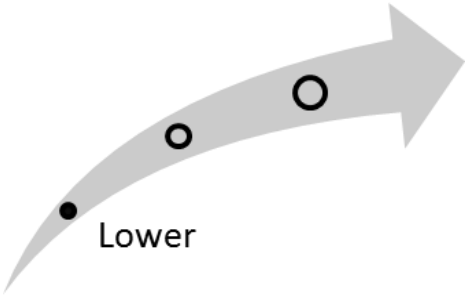
Manufacturer and regulatory status: Ardea Biosciences, San Diego, CA, a wholly owned subsidiary of AstraZeneca PLC, London, UK, makes lesinurad. Lesinurad could be used in combination with xanthine oxidase inhibitors to treat hyperuricemia. Lesinurad could also be used as monotherapy in patients with gout who are intolerant of or who have contraindications for xanthine oxidase inhibitors.[10] The company is preparing regulatory submissions for lesinurad (200 mg) as a once-daily chronic combination therapy for treating gout.[8]

Diffusion and cost: Our searches were unable to find information regarding the expected cost of lesinurad should it be approved. However, according to one financial analyst, sales of lesinurad could reach $582 million by the year 2020.[8] About 10% of patients with chronic gout could be prescribed lesinurad, according to an April 2012 survey of U.S. rheumatologists conducted by health care consultant Decision Resources Group.[11] If approved for marketing, lesinurad will probably be covered by third-party payers similarly to other uric acid-lowering drugs for treating or preventing gout, although if the drug is more costly than alternatives, prior authorization and a tiered approach could be used.

Clinical Pathway at Point of This Intervention

Patients with gout are treated to end the pain of acute flares, prevent future attacks, and prevent formation of tophi and kidney stones.[12] Therapy for acute flares consists of nonsteroidal anti-inflammatory drugs, steroids, and colchicine. Diet and lifestyle modifications (e.g., reducing alcohol and dietary purine intake as well as weight loss) may help prevent future attacks. Preventive therapy with the xanthine oxidase inhibitors allopurinol or febuxostat to lower blood sUA levels is also used in patients with recurrent acute flares or chronic gout.[12] Lesinurad could be used in combination with xanthine oxidase inhibitors for patients in whom sUA levels are inadequately reduced despite therapy or as monotherapy for patients who cannot tolerate or have contraindications to xanthine oxidase inhibitors.[5-7]

Figure 1. Lesinurad for treatment of hyperuricemia and allopurinol-refractory gout



Experts commenting on this intervention stated that a significant unmet need exists for new treatment options to help patients with gout improve the management of their sUA levels. However, the manufacturer could be overestimating this need, because many treatment options are available to address acute flares and for chronic gout management. Still, few agents are available to address the underlying mechanisms leading to gout, the experts thought. Lesinurad demonstrated potential for reducing sUA levels in combination with xanthine oxidase inhibitors or as monotherapy in

patients intolerant to xanthine oxidase inhibitors. The experts warned that lesinurad uptake could be limited by adverse events such as kidney complications, which will continue to be elucidated in ongoing clinical trials. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.[13-18] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A moderate unmet need exists for patients with gout who are unable to reach goal sUA levels, stated the experts. However, one clinical expert warned the unmet need was overstated by the manufacturer, citing 72% of patients in febuxostat clinical trials and 45% of patients on allopurinol achieved desired sUA levels, making the addressable population 28% to 55%.[17] Based on the available data, experts generally thought that lesinurad could address this unmet need by significantly lowering sUA when used in combination with febuxostat or allopurinol or as monotherapy.

Acceptance and adoption: Clinicians are likely to accept lesinurad as a new treatment option to help patients with gout lower their sUA levels, the experts opined. However, one clinical expert and a health systems expert stated that similarities between lesinurad and marketed drugs such as probenecid could reduce lesinurad adoption.[17,18] Patients would likely accept a new treatment option that could help them reduce their sUA if the drug is effective and tolerable and cost to the patient is similar to other agents, the experts thought.

Health care delivery infrastructure and patient management: As an oral medication, lesinurad is not expected to cause a significant shift in health care delivery infrastructure or patient management. However, better gout management could reduce hospitalizations and renal or cardiovascular complications from acute gout flares, reducing demands on the system. Reduced hospitalizations could also provide cost offsets from treatment with lesinurad.[18] One research expert noted concerns over renal adverse events, which could require additional adverse event monitoring while patients are taking lesinurad.[14]

Health disparities: Experts offered mixed comments on the impact of lesinurad on health disparities. Some experts thought that as a new drug, lesinurad could be more expensive than existing options and patients who have trouble affording existing gout treatments would have trouble paying for lesinurad, or payers may not cover a newer, more expensive drug, adding to disparities.[14,15,17,18] However, some experts suspect third-party payers will cover the drug, which would not exacerbate disparities.[16,18] Additionally one expert stated that because a higher incidence of gout is observed in black males, lesinurad could reduce health disparities if more effective treatment options are available.[13]

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